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# Toxoplasmosis: IgG Avidity and Its Implication in Serodiagnosis

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## 1. Introduction

*Toxoplasma gondii* (*T. gondii*) is a ubiquitous, coccidian intracellular protozoan parasite that causes toxoplasmosis, a cosmopolitan zoonosis. *Toxoplasma* infections are reported in approximately one-third of the world's population but most are asymptomatic. The infections are mainly acquired through consumption of raw or uncooked meat containing viable tissue cysts or by contamination with highly resistant oocysts in foods, soil and water. In the symptomatic condition, toxoplasmosis occurs congenitally through transplacental transmission from a primarily infected mother during pregnancy that leads to intrauterine death, spontaneous abortion or severe congenital defects such as retinochoroiditis, hydrocephalus or mental retardation (Wong & Remington, 1994; Tenter et al, 2000; Sukthana, 2006). Toxoplasmosis is also a serious and life-threatening disease found in immunocompromised patients such as in organ transplant recipients (Aubert et al, 1996), patients with cancer (Herold et al, 2009) or AIDS (Nissapatorn et al, 2004).

The laboratory diagnosis of toxoplasmosis can be done in many ways including serology, the isolation of *T. gondii* after inoculation into experimental animals, histological examination, and molecular analysis (Fleck & Kwantes, 1980; Meganathan et al, 2010). Of these, serological tests to determine specific antibodies such as IgG, IgM, IgE or IgA are currently the first-line methods of diagnosis to differentiate recent or chronic infections with *T. gondii* (Sensini, 2006). Diagnosis of symptomatic toxoplasmosis is not straight forward due primarily to the clinical manifestations being varied and it can mimic other diseases (Santoni & Santoni-Williams, 1993; Hurt & Tammara, 2007). Traditionally, the diagnosis of recently acquired toxoplasmosis has been detected either by demonstrating a specific immunoglobulin (Ig) M antibodies, a significant increase in specific IgG antibodies, or both. Due to the high IgG antibodies titres to *T. gondii* infections among the majority of immunocompetents (Remington & Desmonts, 1990) and the persistence of specific IgM antibodies in some individuals this has led to complications in the interpretation of serodiagnostic results even when toxoplasmosis was clinically suspected (Brooks et al, 1987; Bobic et al, 1991; Bertozzi et al, 1999). Moreover, a primary acquired *Toxoplasma* infection during pregnancy and the risk of congenital toxoplasmosis is a medical (clinical and diagnostic) challenge for the clinicians dealing with this tropical and infectious parasitic

disease. Therefore, a sensitive and specific method is mandatory for the management of patients with a high probability of being infected by *T. gondii* (Kotresha & Noordin, 2010). In recent years, a number of new methods including new serodiagnostic tools have been developed towards improving the ability to diagnose recently acquired *Toxoplasma* infections during pregnancy in order to limit congenital infections (CI) in the fetus and newborn (Remington et al, 2004). From this point of view, this chapter is aiming to highlight the significant contributions of recently developed serological methods such as the IgG avidity test and serodiagnosis using various recombinant proteins and its implications for the management, including diagnosis and treatment, of toxoplasmosis, particularly in pregnant women or HIV-infected patients among the so called “high risk” population.

## 2. Recombinant proteins in serodiagnosis of toxoplasmosis

Currently, antigens used for commercial serological assays for the detection of specific anti-*Toxoplasma* antibodies are mainly based on whole tachyzoite lysates. However, the major disadvantage of this kind of antigen is its inconsistent quality due to contamination by extraparasitic components during the processing of preparations that result in interassay variability (Aubert et al, 2000). The use of recombinant antigens cloned in suitable expression vectors has been proven to improve consistency of the tests and to reduce the costs of production (Hiszczyjska-Sawicka et al, 2003). However, because of its complex life cycle, a number of proteins produced at different stages of the parasite life cycle can play different roles in stimulating host immune responses during the infectious process. Furthermore, a precise distinction between acute and latent invasion may be difficult since IgM antibodies, a specific marker for early infection, could be present in sera for many years (Meek et al, 2001). Therefore, certain antigens that are specific to the acute or chronic stages of the infection that produce specific IgG antibodies could serve as a mean to distinguish the recent from a chronic infection.

Tachyzoites, the rapidly multiplying stage of the parasite, is considered to be responsible for active toxoplasmosis. In contrast, bradyzoites, a dormant stage that persists within cysts and is thought to evade the immune response by their absence of expression of immunodominant antigens throughout a prolonged infection (Smith et al, 1996). Several studies have shown that the main targets for antibody production during the acute and chronic phase of *Toxoplasma* infection are the surface antigens (SAG) present in the tachyzoite membrane (Mineo et al, 1980) and their usefulness as antigens has been shown. Secretory proteins: micronemes (MIC), rhoptries (ROP) and dense granules (GRA) released from three distinct tachyzoite parasite organelles during invasion are other potential diagnostic antigens of interest as markers of acute infection. ROP and MIC released during the cell invasion, and GRA that is discharged from parasitophorous vacuoles after invasion, and continues during the intracellular residence of the organism (Carruthers & Sibley, 1997).

The usefulness of several recombinant antigens of *T. gondii* that have been produced and extensively evaluated for their potential use as diagnostic antigens in ELISA to detect specific IgG antibodies during the early phase of infection, allows for differentiation of an acute from a chronic infection. Furthermore, if only a single serum sample is available, an IgG avidity test using recombinant antigens is seen to be more appropriate for detecting a recently acquired infection. The sensitivity and specificity for these antigens have been reported to be in the range of 80% to 100%. These antigens have included:

## 2.1 Rhoptries antigens (ROP)

Rhoptries are unique secretory organelles shared by all Apicomplexan invasive stages. More than 30 ROPs of *T. gondii* have been identified (Bradley et al, 2005). They are exocytosed upon host cell invasion and their contents are involved in many functions fundamental for the parasite to enter into host cells, and for the establishment and maintenance of the parasitophorous vacuole membrane and acquisition of nutrients (Dubremetz, 2007). The use of recombinant ROP antigens (rROP) has been largely described as the antigenic substrate to use in ELISA tests to detect infection with *T. gondii* (vanGelder et al, 1993; Aubert et al, 2000; Chang et al, 2011). rROP1 has shown its diagnostic value in IgG ELISA avidity tests for identification of acute infections (Holec-Gąsior et al, 2009, 2010a). There is data regarding the potential use of rROP2 for the diagnosis of acute toxoplasmosis that have focused on IgG reactivities (Martin et al, 1998; Chang et al, 2011). In a mouse model, IgM antibody against rROP4 was significantly higher than IgG antibodies with a peak of detection coming on the turn of the acute to a latent infection (Gatkowska et al, 2010).

## 2.2 Microneme proteins (MIC)

MICs are proteins involved in recognition and/or binding to the host cell (Soldati et al, 2001). At least 12 MICs have been identified from *T. gondii* (Carruthers & Tomley, 2008). However, little is known whether rMIC can be used as an antigen. rMIC1 has thus far been the only protein shown to be highly reactive against sera of patients with acute toxoplasmosis (Holec et al, 2008).

## 2.3 Dense granule antigens (GRA)

Among identified GRA antigens, at least 12 out of 14 GRA antigens have been detected from *T. gondii* tachyzoites as excretory/secretory antigens (Nam, 2009). They are believed to be involved in parasite survival and virulence (Michelin et al, 2009; Rome et al, 2008). GRA1 is the major secretory antigen recognized in humans chronically infected with *Toxoplasma*. GRA2 has been shown to induce strong antibody and T-cell responses in both humans and experimental mice (Sharma et al, 1984; Brinkmann et al, 1993; Murray et al, 1993; Prigione et al, 2000). While, GRA6 and GRA7 are also shown strong antibody responses in the acute phase of *Toxoplasma* infection (Gatkowska et al, 2006). GRA7 was found in the parasitophorous vacuole and cytoplasm of the host cell infected with the tachyzoite stage (Jacobs et al, 1998). As a consequence, GRA7 is only released after the rupture of infected cells in the acute stage of infection and it is only then that it is exposed to the hosts' immune system. Therefore, detection of GRA7 antibodies would be expected to be a good candidate to use for serodiagnosis. Several rGRA antigens such as rGRA2 (Golkar et al, 2007; Holec-Gąsior et al, 2009), rGRA6 (Aubert et al, 2000; Golkar et al, 2008), rGRA7 (Aubert et al, 2000; Pietkiewicz et al, 2004; Pfrepper et al, 2005; Pietkiewicz et al, 2007), and rGRA8 (Pfrepper et al, 2005; Gatkowska et al, 2006; Babaie et al, 2009) have been proposed as markers to indicate acute infections. rGRA4 and rGRA7, but not rROP2, have been shown to be valuable in differentiating acute and chronically infected individuals for both adult and congenital toxoplasmosis (Nigro et al, 2003; Altcheh et al, 2006). In contrast, rGRA1 was reported to be a marker for chronic infections (Ferrandiz et al, 2004; Pietkiewicz et al, 2004).

2.4 Surface antigens (SAG)

Five major SAG antigens specific to the tachyzoite stage have been identified (Couvreur et al, 1988). Of these, the SAG1, SAG2, and SAG3 antigens are the main proteins expressed on the surface of tachyzoites. They are involved in the process of host cell invasion after infection (Mineo & Kasper, 1994; Grimwood & Smith, 1996), and are highly immunogenic for IgG responses. SAG1 and SAG3 are stage-specific antigens of the tachyzoites and are highly conserved in most isolates (Gross et al, 1996; Wu et al, 2009). In contrast, SAG2 has been identified from both bradyzoites and tachyzoites (Lekutis et al, 2000). SAG4 is another surface protein that is specifically expressed by bradyzoites (Knoll & Boothroyd, 1998). rSAG1 successfully detected IgG antibodies in the acute phase of infection (Pietkiewicz et al, 2004), but the highest response to rSAG1 was found during latent infections (Gatkowska et al, 2010). Some studies did show that rSAG2 was effective in specifically detecting IgG antibody to *T. gondii* in patients with acute toxoplasmosis (Parmley et al, 1992). However, more recent studies showed that rSAG2 was produced in acute and chronic infections (Lau & Fong, 2008), whereas rSAG2A was present only during the acute phase of toxoplasmosis (Béla et al, 2008).

2.5 Combinations of recombinant antigens

A cocktail of recombinant antigens help to improve the serological diagnosis of clinical toxoplasmosis. A combination of rGRA1 and rGRA6 has shown promising results when being preliminary tested (Lecordier, 2000). While, the triple combination of SAG1, ROP1 and GRA7 have also been successfully tested in a preliminary format (Aubert, 2000). Different combinations of recombinant antigens that have been evaluated and successfully increase the sensitivity of serodiagnosis from chronic toxoplasmosis are summarized in Table 1.

References	Combinations of recombinant antigens
Aubert et al, 2000	rSAG1, rROP1, and rGRA7 rGRA7, rGRA8, and rSAG1
Li et al, 2000	rGRA7, rGRA8, rSAG2, and rH4
Nigro et al, 2003	rROP2 and rGRA7
Pietkiewicz et al, 2004	rSAG1, rGRA1, and rGRA7
Holec et al, 2008	rGRA1, rGRA7, and rSAG1 rGRA8, rSAG2, and rGRA6 rMic1ex2, rMAG1, and rMIC3
Cóceres et al, 2010	rHSP20, rSAG1, and rGRA7 rHSP20 and rSAG1 rHSP20 and rGRA7 rSAG1 and rGRA7
Holec-Gąsior & Kur, 2010	rMAG1, rSAG1, and rGRA5 rGRA2, rSAG1, and rGRA5 rROP1, rSAG1, and rGRA5
Holec-Gąsior et al, 2010b	rMAG1 + rSAG1 + rGRA7

Table 1. Selected combination of recombinant antigens that increase the sensitivity of serodiagnosis of chronic toxoplasmosis.



Furthermore, the multiple combinations of recombinant antigens P22, P25, P29, and P35 has confirmed that a cocktail of antigens might be helpful to differentiate between acute and chronic infections when tested against specific IgG antibodies in human samples (Li, 2000). Based on these results, it clearly shows that the combination of recombinant antigens is mandatory in the attempt to distinguish between acute and chronic *Toxoplasma* infections. Nonetheless, the combination of GRA1 and GRA6 for distinguishing between acute and chronic infections was unsuccessful found in pregnant women (Ferrandiz et al., 2004). The combinations of recombinant antigens that could be used to distinguish between acute and chronic infections are summarized in Table 2.

References	Combinations of recombinant antigens
Li et al, 2000	rGRA8, rSAG2, rGRA2, and rGRA7
Beghetto et al, 2003	rGRA3, rGRA7, rMIC3, and rSAG1
Pietkiewicz et al, 2007	rGRA1, rGRA7 and rSAG1

Table 2. Selected combination of recombinant antigens that use to distinguish between acute and chronic infections.

3. IgG-avidity: A real-time serodiagnosis for *Toxoplasma* infection

It seems that a conventional single serum assay does not provide an accurate diagnosis in differentiating between a recently acquired primary infection and a chronic infection (Lappalainen & Hedman, 2004). The IgG-avidity test is an assay that measures the antigen-binding avidity/affinity of IgG antibodies against *T. gondii* infection and was first introduced to try to eliminate this problem (Hedman et al, 1989). This avidity test has significantly lessened the possibility of misdiagnosis, by assisting in determining a difference between a recently acquired (primary/acute) and a chronic (latent/past/remote) infection. This has greatly decreased the requirement for a confirmatory (a single or the first sample) or follow-up serological tests, to remove any doubts or anxiety for further testings (Cozon et al, 1998; Liesenfeld et al, 2001; Montoya et al, 2002; Remington et al, 2004; Press et al, 2005; Reis et al, 2006; Candolfi et al, 2007; Nissapatorn et al, 2011). Hence, the measurement of IgG-avidity has proved to be a highly sensitive method, used to assess the early time of antigenic challenge and it is especially recommended for use in combination with other existing conventional serological assays (Lappalainen & Hedman, 2004; Nissapatorn et al, 2011). The IgG avidity test has so far been the best serological approach that can offer a rapid diagnosis of a recently acquired *Toxoplasma* infection in a single serum sample. Until now the IgG-avidity test has been tested and used in several different clinical scenarios: a recently acquired *Toxoplasma* infection, primary acquired infection during pregnancy, congenital toxoplasmosis, ocular toxoplasmosis (OT), and in immunocompromised individuals such as cancer patients, solid organ transplant recipients or persons living with HIV/ AIDS.

3.1 Acute (recently) acquired *Toxoplasma* infection

Approximately, one-third of the world’s populations are infected with *T. gondii*. However, the majority of these are either mild with non-specific clinical symptoms or asymptomatic. Lymphadenopathy is significantly present in only 3-7% of clinical cases but is the most common form in immunocompetent individuals (Gard & Magnusson, 1951; McCabe et al, 1987). The clinical features show localized, nontender and nonsuppurative lymphadenopathy

as a result of *Toxoplasma* infection. Of note, lymphadenopathy may persist for months and may mimic clinically or histologically with neoplastic diseases such as lymphoma or carcinoma of the head, neck and breast (Lappalainen & Hedman, 2004). The diagnosis of toxoplasmic lymphadenopathy is based on serology and lymphnode biopsy.

Serological techniques have traditionally been used but shown some limitations in evaluating the timing of *Toxoplasma* infections. The IgG avidity test has since been introduced for differentiation between recently acquired and past infections in the course of toxoplasmic lymphadenopathy. The duration of low avidity values in patients with lymphadenopathy is not well defined. Lecolier and Pucheu observed patients whose sera had a low IgG avidity for as long as 20 weeks after the acquisition of infection (Lecolier & Pucheu, 1993). A low IgG avidity occurs during < 3 months of lymphadenopathy (Holliman et al, 1994). In the present study, low IgG avidity values were still observed 5 months after the first serological examination in 6 of 19 patients (31.6%) with lymphadenopathy (Paul, 1999). Whereas, a high IgG avidity test resulted from an individual who had a recent onset of lymphadenopathy of at least 4 months (Montoya et al, 2004). Therefore, a high IgG avidity value strongly excludes a recent infection, that is, one that was acquired during the previous 5 months, but a low avidity is not a safe marker for an early stage of infection (Paul, 1999).

### 3.2 Primary acquired *Toxoplasma* infection during pregnancy

Based on epidemiological data, the prevalent rate of *Toxoplasma* infection in pregnant women is generally high in many geographical locations and plausible risk factors play an important role in *Toxoplasma* acquisition found among these women. However, the rate of acute (recent) acquired *Toxoplasma* infection is unexpectedly low in pregnant women. The gestational stages of pregnancy are determined by the impacts of vertical transmission from the infected mother to the fetus; primary *Toxoplasma* infection in early trimester of pregnancy may result in severe clinical disease, in contrast, congenital toxoplasmosis as a result of maternal infection during third trimester of pregnancy is usually subclinical at birth (Desmonts, 1979). The clinical symptoms of acute toxoplasmosis during pregnancy are usually subclinical or associated with non-specific symptoms. Therefore, the diagnosis is mainly based on serological responses of pregnant women. Serological results are however difficult to interpret and that has contributed to the most challenging situation during pregnancy.

In clinical practice, simultaneous testing for specific IgG and IgM antibodies against *T. gondii* in serial serum samples collected at an interval of 3 weeks is the early step in routine screening for *Toxoplasma* infection. Of note, the presence of specific IgG and/or IgM antibodies against *T. gondii* in a single serum sample drawn during pregnancy cannot be used to determine if the infection was chronic or recently acquired. Therefore, successive tests and the definitive diagnosis are required as a result of this initial screening. Factors such as the trimester of infection and maternal-neonatal therapeutic treatments are the main contributing factors to the variation of immunological responses of both mother and neonate (Sensini, 2006). Early and accurate diagnosis is crucial during pregnancy, as the women then require immediate therapeutic options. In addition, IgG and IgM antibodies against *T. gondii* are the first-line serological diagnosis for the detection of recent or chronic infections. A seropositive woman for only IgG antibodies, is unlikely to have recently acquired

toxoplasmosis due to the level of specific *Toxoplasma*-IgG antibodies which is an unreliable indicator for acute infection (Robert et al, 2001). Following an acute *Toxoplasma* infection in the mother, the evidence for a rapidly transmitted infection to the fetus has been observed. Hence, early diagnosis of an acute infection during pregnancy is crucial to determine whether treatment of the infected mother can prevent vertical transmission to the fetus.

The measurement of IgG avidity has been developed to avoid using confirmatory tests from a second serum sample for the possibility of a recently acquired infection obtained from the initial serodiagnostic test. A specific positive IgG test with a low avidity has been used to confirm a recent primary acquired *Toxoplasma* infection by using a single serum indicator (Joynson et al, 1990; Lappalainen et al, 1993; Holliman et al, 1994; Jenum et al, 1997; Liesenfeld et al, 2001; Roberts et al, 2001; Abdel Hameed & Helmy, 2004; Press et al, 2005; Reis et al, 2006; Nissapatorn et al, 2011). Due to it being a safe and useful tool for screening for high sensitivity, an IgG-avidity test is able to verify that the majority of pregnant women who presented with *Toxoplasma* IgM antibodies did not have a recently acquired infection (Lappalainen et al, 1993; Nissapatorn et al, 2011). IgG-avidity is therefore recommended to serve as the primary tool for an IgG assay and a sensitive IgM test (Lappalainen & Hedman, 2004; Olariu et al, 2006). Moreover, the IgG-avidity test can be used as a subsequent measurement to confirm the IgM diagnosis, as shown in suspected cases of acute recent toxoplasmosis in immunocompetent patients (Table 3).

Clinical scenarios	Diagnostic tests
<b>Immunocompetents</b>	
Acute infection (primary acquired infection)	<i>Toxoplasma</i> -IgG and <i>Toxoplasma</i> -IgM antibodies, followed by the measurement of IgG-avidity test (if <i>Toxoplasma</i> -IgM positive)
Immunity (latent/chronic/past infection)	<i>Toxoplasma</i> -IgG antibodies
Ocular toxoplasmosis (acute retinochoroiditis)	<i>Toxoplasma</i> -IgG and <i>Toxoplasma</i> -IgM antibodies for the detection of past exposure; seldom useful to show acute infection.
Congenital toxoplasmosis (maternal-fetal infection)	Serology for <i>Toxoplasma</i> -IgG, -IgM and -IgA antibodies of the newborn and the mother. <i>Toxoplasma</i> -PCR (and culture, if available) from clinical specimens such as blood, urine and cerebrospinal fluid (CSF).
<b>Immunosuppressed patients</b> (cancer patients, organs transplant or HIV-infected patients)	<i>Toxoplasma</i> -IgG and <i>Toxoplasma</i> -IgM antibodies for the detection of past exposure; a second sample is needed to show reactivation. <i>Toxoplasma</i> -PCR (and culture, if available) to detect ongoing active infection using blood and CSF specimens.

Table 3. Laboratory diagnosis in different clinical scenarios of toxoplasmosis.

When a primary acquired infection in a pregnant mother is diagnosed either by seroconversion for IgG or being seropositive for IgM antibodies followed by a low IgG-avidity, the infected mother should be referred immediately for medical assessment to an obstetrician who should include further tests including molecular analysis using an amniotic fluid sample to determine any fetal infection (Hohlfeld et al, 1994; Jenum et al,



References	Sero-pattern	Interpretation	Comments
Montoya & Liesenfeld, 2004 National committee for clinical laboratory standard, 2004 Remington et al, 2004 Nissapatorn et al, 2011	IgG+IgM+ Mother	(a) Past or recently acquired infection	<ul style="list-style-type: none"><li>• Risk for congenital infection (CI)</li><li>• Take gestation period into account. Serological tests for specific <i>Toxoplasma</i>-IgA and -IgE antibodies and IgG-avidity</li></ul>
		(b) False-positive	<ul style="list-style-type: none"><li>• No risk for CI</li><li>• Serological tests for specific <i>Toxoplasma</i>-IgA and -IgE antibodies and IgG-avidity</li></ul>
Sharma et al, 1983 Partanen et al, 1984 Villena et al, 1999 Gross et al, 2000 Pinon et al, 2001 Remington et al, 2001 Montoya, 2002 Flori et al, 2004 Nielsen et al, 2005	IgG+IgM+ Newborn	(a) Maternal antibodies	<ul style="list-style-type: none"><li>• No risk for CI</li><li>• Collect 2<sup>nd</sup> serum sample 10 days after birth to confirm contaminating maternal specific <i>Toxoplasma</i>-IgM antibodies. Test in parallel maternal and neonatal specific <i>Toxoplasma</i>-IgG antibodies by Western blotting (WB) or ELISA. Serological follow-up for 1 year to confirm seronegativity for specific <i>Toxoplasma</i>-IgG antibodies.</li><li>• Check for stable IgG-avidity index.</li></ul>
		(b) Maternal and neonatal antibodies	<ul style="list-style-type: none"><li>• CI after maternal infection in the third trimester (IgA+) or in the last month (IgA-) of pregnancy</li><li>• Collect 2<sup>nd</sup> serum sample 10 days after birth in parallel maternal and neonatal specific IgG antibodies by WB or ELISA. Serological follow-up for 1 year to demonstrate the persistence of specific <i>Toxoplasma</i>-IgG antibodies.</li><li>• Check for increased IgG-avidity index</li></ul>

Table 4. The measurement of IgG avidity test for toxoplasmosis in pregnant woman and newborn.

1998). The combination of a sensitive test for *Toxoplasma*-specific IgM antibodies and the measurement of IgG avidity had shown the highest predictive value in association with the possible time of infection (Petersen et al, 2005; Press et al, 2005). When a high IgG-avidity result was found in women within their first trimester of pregnancies, it provided a strong indicator against primary infection. As there is a low risk of congenital toxoplasmosis there is no intervention necessarily required. In general, IgG-avidity has been used to confirm past or recently acquired infection or false-positive results in pregnant women who showed seropositive for IgG and IgM antibodies (Table 4) and this has been recommended by several authors (Montoya & Liesenfeld, 2004; National committee for clinical laboratory standard, 2004; Remington et al, 2004).

### 3.3 Congenital toxoplasmosis

Toxoplasmosis has historically been recognized as one of the most important pathogens causing congenital infection (CI) and it has also been comprised in “TORCHs” infections. Transplacental (vertical, congenital, materno-fetal) transmission of *T. gondii* can be a serious complication as a result of primary acquired infection during pregnancy. Of note, most infected children are asymptomatic at birth but they can manifest problems during later decades of life associated with ocular (acute retinochoroiditis) and neurological involvements (hydrocephalus).

Postnatal diagnosis is a complex process due to the presence of passive maternal IgG antibodies or the variability of perinatal IgM antibody findings (Desmonts et al, 1985; Daffos et al, 1988). Moreover, the level of specific IgA and IgM antibodies may not be able to be detected in all children with CI. Hence, a combination of specific IgA and IgM antibodies is the recommended approach for serological measurements in affected children (Naessens et al, 1999). In addition, determination of IgG-avidity and/or serological detection of specific IgG could serve as an alternative option for the diagnosis of congenital toxoplasmosis (Said et al, 2011). Combined with serological tests, the role of PCR in detecting *T. gondii* organism in amniotic fluid sample has been found to be more promising in terms of sensitivity and specificity during antenatal testing compared to postnatal diagnosis (Hohlfeld et al, 1994; Jennum et al, 1998; Yamada et al, 2011).

IgG avidity is generally not tested in the neonate due primarily to its having a similar pattern to the infected mother. However, a previous study has demonstrated that a significant maturation of IgG avidity was shown in congenitally infected children during postnatal follow-up (Lappalainen et al, 1995). In contrast, long-term therapy with pyrimethamine-sulphonamide, as opposed to treatment with spiramycin alone, was found to slow the progression of the avidity index (Flori et al, 2004). An IgG-avidity result in the first month of the postnatal period usually represents a combination of both mother and the newborn's own IgG antibodies and that depends on several contributing factors such as the sampling time, the IgG-titre and avidity of the mother as well as the newborn (Lappalainen & Hedman, 2004). In the absence of maternofetal transmission, the avidity index remains stable until the disappearance of passively transmitted specific antibodies from the infected mothers (Sensini, 2006). It is of interest that there is a delay of maturation of IgG-avidity in congenital toxoplasmosis that can be demonstrated by performing the test on antibodies eluted from dried blood spots (Guthrie cards) to detect, at birth, a maternal primary infection acquired during the second or third trimester of pregnancy and to evaluate retrospectively the risk for high suspicion of CI during late infancy (Buffolano et al, 2004). In

general, it has been recommended that IgG-avidity should be used to confirm CI in the neonates (Table 4) being seropositive for both IgG and IgM antibodies either from maternal antibodies or both maternal and neonatal antibodies (Sharma et al, 1983; Weiss et al, 1988; Chumpitazi et al, 1995; Flori et al, 2004; Nielsen et al, 2005).

### 3.4 Ocular toxoplasmosis

Ocular toxoplasmosis (OT) occurs mainly in the uveal tract and it is the most common cause of posterior uveitis in immunocompetent persons. Retinochoroiditis is the most common lesion found among non-specific clinical manifestations of OT. In most cases, OT is the result of reactivated or congenital rather than from acquired *Toxoplasma* infections (Perkins, 1973; Ronday et al, 1995; Montoya & Remington, 1996). Clinical diagnosis of OT is based on the manifestations of characteristic biomicroscopic features (Rothova et al, 1986; de Jong, 1989; Tabbara, 1994).

Over more than three decades, many different serological tests have been introduced to detect specific IgG antibodies against *T. gondii* that can indicate chronic infections (Holliman et al, 1991). The detection of specific IgM antibodies indicates a recently acquired infection, however, it is found to have a high rate of false-positive results due to persisting IgM antibodies (Leisenfeld et al, 1997). Moreover, the absence or low levels of specific IgM antibodies in reactivated OT, cannot therefore serve as a reliable serological marker for this disease (Lappin et al, 1995; Ronday et al, 1995; Garweg et al, 1998; Klaren et al, 1998). Serological diagnosis of OT is insensitive (Rothova et al, 1986; Kijlstra et al, 1989; Holliman et al, 1991) and is of limited value (Lappalainen & Hedman, 2004). Also, the role of an IgG avidity measurement is to confirm the stage of chronic infection and to raise the suspicion of an ongoing reactivated OT (Paul, 1999; Garweg et al, 2000).

### 3.5 Cerebral toxoplasmosis

In contrast to the majority of immunocompetent persons, toxoplasmosis can cause serious clinical outcomes in immunocompromised individuals such as patients with AIDS or organ transplant recipients. In patients with an advanced HIV infection, toxoplasmosis is one of the most common central nervous system diseases associated with opportunistic infections that cause high rates of morbidity and mortality. Cerebral toxoplasmosis (CT) is the most common clinical disease entity and it causes focal intracerebral lesion(s) in patients with AIDS. Among AIDS patients, >95% of CT is due to the reactivation of latent (chronic) *Toxoplasma* infections as a result of the progressive loss of cellular immunity (Luft & Remington, 1988). In clinical practice, the incidence of CT patients is related both to *Toxoplasma* IgG seropositivity and to the CD4 cell count. The risk of developing CT among seropositive patients with AIDS was 27 times that of seronegative ones (Oksenhendler et al, 1994). The clinical presentations of CT depend on the number of lesions and locations. Headache, hemiparesis and seizure (Porter & Sande, 1992; Nissapatorn et al, 2004; Vidal et al, 2005) are among the most common neurological presentations found in CT patients. Other clinical manifestations include disarthria, movement disorders, memory and cognitive impairments and neuropsychiatric abnormalities. These neurological deficits remain in surviving patients even after a good clinical response to therapy (Hoffmann et al, 2007). More than 50% of CT patients may have focal neurological findings. The empirical diagnosis is based on a low CD4 count of less than 200 cells/cumm, computer tomography scans will show ring enhancing lesions, seroevidence of specific IgG, IgM or both antibodies

to *T. gondii*, and a good response to anti-*Toxoplasma* therapy. Specific anti-*Toxoplasma* therapy is initiated in a highly suspicious or confirmed toxoplasmosis. CT is a life-threatening but treatable condition provided there is early diagnosis and treatment.

In HIV-infected patients, serological titres are often low and that makes for disease phase definition and therapeutic decisions difficult (Spausta et al, 2003). The determination of IgG avidity is another serological marker and it has been shown to be of some help in serodiagnosis of *Toxoplasma* infection among immunocompromised individuals. So far, very few studies have used the IgG avidity test for the differentiation of primary and reactivated chronic infections in HIV-infected patients. However, there was no significant difference between the avidity values in HIV-infected patients with CT and those without clinical signs of reactivation (Holliman et al, 1994; Spausta et al, 2003; Adurthi et al, 2010). A liver transplant recipient with reactivated toxoplasmosis was first reported by performing an IgG avidity test (Lappalainen et al, 1998). This patient was seropositive for *T. gondii* with high avidity indicating a chronic infection before the first transplantation. Subsequently, serological diagnosis showed a rise in specific IgG antibodies, negative for IgM antibodies and with a constantly high IgG avidity, indicating a reactivation before the second transplantation. Serodiagnosis for *T. gondii* was negative for both donors. The presence of *T. gondii* DNA was shown by PCR in blood samples and liver biopsy prior to the death of this patient. Based on the results obtained, an avidity test for the serological status of *T. gondii* is therefore recommended if there are non-specific clinical symptoms of toxoplasmosis and it could be used for the diagnosis in differentiating recently acquired, chronic or secondary reactivation of latent toxoplasmosis in immunocompromised patients.

#### 4. Conclusion

Estimation of the IgG avidity index is a classical serological method. Antibodies with low avidity are detectable at a very early stage of infection whereas high avidity antibodies indicate past infections. The measurement of IgG avidity has demonstrated its superior diagnostic values in serological interpretations of *Toxoplasma* infections in different clinical scenarios, particularly when timing between chronic and recently acquired infections or primary and secondary (reactivated) infections are required. The IgG avidity test represents an important addition to other first-line serological methods such as IgG, IgM and IgA specific antibodies against *T. gondii*. Above all, serological diagnosis should be performed in combination with culture based and molecular techniques to obtain the best and most accurate results.

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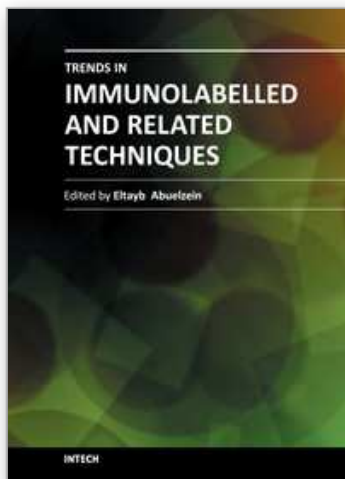
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## **Trends in Immunolabelled and Related Techniques**

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The book is coined to provide a professional insight into the different trends of immunoassay and related techniques. It encompasses 22 chapters which are grouped into two sections. The first section consists of articles dealing with emerging uni-and-multiplex immunolabelled methods employed in the various areas of research. The second section includes review articles which introduce the researchers to some immunolabelled techniques which are of vital significance such as the use of the conjugates of the Staphylococcus aureus protein "A" and the Streptococcus Spps. protein "G" in immunolabelled assay systems, the use of bead-based assays and an overview on the laboratory assay systems. The book provides technological innovations that are expected to provide an efficient channel for developments in immunolabelled and related techniques. It is also most useful for researchers and post-graduate students, in all fields, where immunolabelled techniques are applicable.

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